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Abstract: BACKGROUND Long-term survival of patients with a single ventricle palliated with a Fontan procedure is still limited. No curative treatment options are available. To investigate the pathophysiology and potential treatment options, such as mechanical circulatory support (MCS), appropriate large animal models are required. The aim of this review was to analyze all full-text manuscripts presenting approaches for an extracardiac total cavopulmonary connection (TCPC) animal model to identify the feasibility and limitations in the acute and chronic setting. METHODS A literature search was performed for full-text publications presenting large animal models with extracardiac TCPCs on Pubmed and Embase. Out of 454 reviewed papers, 23 manuscripts fulfilled the inclusion criteria. Surgical procedures were categorized and hemodynamic changes at the transition from the biventricular to the univentricular condition analyzed. RESULTS Surgical procedures varied especially regarding coronary venous flow handling and anatomic shape of the TCPC. In most studies (n = 14), the main pulmonary artery was clamped and the coronary venous flow redirected by additional surgical interventions. Only in five reports, the caval veins were connected to the right pulmonary artery to create a true TCPC shape, whereas in all others (n = 18), the veins were connected to the main pulmonary artery. An elevated pulmonary vascular resistance was identified as a limiting hemodynamic factor for TCPC completion in healthy animals. CONCLUSIONS A variety of acute TCPC animal models were successfully established with and without MCS, reflecting the most important hemodynamic features of a Fontan circulation; however, chronic animal models were not reported.

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Approaches to Establish Extracardiac Total Cavopulmonary Connections in Animal Models—A Review

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Abstract

Background: Long-term survival of patients with a single ventricle palliated with a Fontan procedure is still limited. No curative treatment options are available. To investigate the pathophysiology and potential treatment options, such as mechanical circulatory support (MCS), appropriate large animal models are required. The aim of this review was to analyze all full-text manuscripts presenting approaches for an extracardiac total cavopulmonary connection (TCPC) animal model to identify the feasibility and limitations in the acute and chronic setting. **Methods:** A literature search was performed for full-text publications presenting large animal models with extracardiac TCPCs on Pubmed and Embase. Out of 454 reviewed papers, 23 manuscripts fulfilled the inclusion criteria. Surgical procedures were categorized and hemodynamic changes at the transition from the biventricular to the univentricular condition analyzed. **Results:** Surgical procedures varied especially regarding coronary venous flow handling and anatomic shape of the TCPC. In most studies (n = 14), the main pulmonary artery was clamped and the coronary venous flow redirected by additional surgical interventions. Only in five reports, the caval veins were connected to the right pulmonary artery to create a true TCPC shape, whereas in all others (n = 18), the veins were connected to the main pulmonary artery. An elevated pulmonary vascular resistance was identified as a limiting hemodynamic factor for TCPC completion in healthy animals. **Conclusions:** A variety of acute TCPC animal models were successfully established with and without MCS, reflecting the most important hemodynamic features of a Fontan circulation; however, chronic animal models were not reported.

Keywords

animal model, Fontan, circulatory assistance, CHD, univentricular heart, cavopulmonary anastomosis

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Introduction

In children born with complex congenital heart diseases and single ventricle physiology, therapeutic options are limited.[1] While the absence of an intervention will inevitably lead to a significantly limited life span with continuous cyanosis and evolving heart failure, other options are primary heart transplantation or the so-called "Fontan procedure". Whereas the availability of donor organs especially for children is limited, surgical creation of the Fontan circulation offers a perspective with acceptable quality of life for several years.[2–4] Nowadays, in most patients with a single functional ventricle, the total cavopulmonary connection (TCPC) is completed by a superior cavopulmonary anastomosis in combination with an extracardiac conduit interposition between the inferior vena cava (IVC) and the superior vena cava (SVC)/pulmonary artery (PA) amalgamation in a cross-like fashion. With this modification, the procedure got simplified and long-term morbidity could be reduced in comparison to earlier approaches.[4–6] Despite this, patients still experience a multiplicity of cardiovascular complications. In many patients, the Fontan circulation fails at a certain time point, earlier than in

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Abbreviations and Acronyms

ASD	atrial septum defect
BSA	body surface area
BW	body weight
CO	cardiac output
CPB	cardiopulmonary bypass
CVP	central venous pressure
IVC	inferior vena cava
LAP	left atrial pressure
MAP	mean arterial pressure
MCS	mechanical circulatory support
PA	pulmonary artery
PAP	pulmonary arterial pressure
PVR	pulmonary vascular resistance
RA	right atrium
RV	right ventricle
SVC	superior vena cava
SVR	systemic vascular resistance
TCPC	total cavopulmonary connection
TVR	total vascular resistance

an age-matched normal population.[7] The causes for the cardiovascular failure are multifactorial and include increased pulmonary vascular resistance (PVR), diastolic and/or systolic dysfunction of the systemic ventricle, lymphatic as well as hepatic dysfunction, development of collaterals, and others.[7] Clinical insights into invasive hemodynamics are scarce and alternatives like chronic animal models with an extracardiac TCPC are not yet available.

To systematically address this challenge, a review was performed to identify the limiting factors of current models and to find potential solutions. This review presents and analyzes full-text publications reporting extracardiac TCPCs in animals with and without mechanical circulatory support (MCS).

Materials and Methods

Search Strategy

A systematic literature search for relevant full-text publications in English or German was conducted on the electronic databases PubMed and EMBASE on May 6, 2017. The following search terms were used: "animal" AND ("Fontan" OR "TCPC" OR "Total cavopulmonary connection" OR "right heart bypass"). The publication year was limited from January 1, 1990, to May 6, 2017. In addition to the electronic databases, the reference lists of the finally included papers were screened for studies of interest.

Screening of Studies and Inclusion Criteria

The aim of this review was to identify all studies reporting surgical completion of an extracardiac TCPC with or without MCS in a large animal model.

To select the appropriate studies, the following inclusion and exclusion criteria were defined:

Table 1. Outcome Variables of the Review.

Animals	• Species • Age • Number • Weight • Body surface area (BSA)
Surgical technique	• Type and shape of TCPC • Coronary flow handling • Cardiopulmonary bypass required • Position of implanted MCS system
Hemodynamic parameters	• Mean arterial pressure (MAP) • Central venous pressure (CVP) • Pulmonary arterial pressure (PAP) • Left atrial pressure (LAP) • Cardiac output (CO) • Pulmonary vascular resistance (PVR) • Systemic vascular resistance (SVR)

Abbreviations: MCS, mechanical circulatory support; TCPC, total cavopulmonary connection.

- The inclusion criteria were an experimental accomplishment of an extracardiac TCPC (extracardiac conduit connection between IVC and the SVC/PA) in a large acute or chronic animal model reported in a full-text paper in English or German with at least partially original results.
- Exclusion criteria were clinical trials, retrospective analyses, reviews, in vitro and in silico studies, experiments with small animals, intra-atrial TCPCs, and other forms of cavopulmonary connections such as the interposition of an extracardiac conduit between the right atrium (RA) and the pulmonary arteries, Glenn, or Norwood I and II.

No restrictions were applied to age or species of the large animals. Studies with an extracardiac TCPC with or without cavopulmonary and/or ventricular MCS were included.

In a first step, two experts screened the titles and abstracts of all studies independently. Each study was considered eligible if it matched the inclusion criteria. Adequacy of description of the surgical procedure was also important to determine inclusion or exclusion. In a next step, the full texts of the remaining studies were analyzed to determine definite selection. Discrepancies between the experts' opinions were resolved by discussion and consensus.

Data Extraction and Analysis

The parameters listed in Table 1 were extracted from the selected papers (if available).

If possible, missing hemodynamic parameters of those listed above were derived from the central venous pressure (CVP), the cardiac output (CO), the left atrial pressure (LAP), the mean pulmonary arterial pressure (PAP), systemic vascular resistance (SVR), PVR, the mean arterial pressure (MAP), and total vascular resistances (TVRs) by making use of basic hemodynamic principles:

$$\mathrm{MAP} - \mathrm{CVP} = \mathrm{SVR} \times \mathrm{CO},$$

$$\mathrm{PAP} - \mathrm{LAP} = \mathrm{PVR} \times \mathrm{CO},$$

$$\mathrm{TVR} = \mathrm{SVR} + \mathrm{PVR}.$$

Hemodynamic values normalized for body surface area (BSA) or body weight (BW) were converted to their original value using either the reported BSA or the BSA that was estimated based on the BW of the animals.[8,9]

Statistical Methods

The hemodynamic parameters presented in Table 1 were collected from the included studies. To quantify differences for each of these outcome variables, the pooled mean percentage change ($\bar{m}$) between the biventricular and the univentricular condition was calculated:

$$\bar{m} = \frac{\sum_{j=1}^{k} m_j n_j}{\sum_{j=1}^{k} n_j},$$

where m_j is the mean percentage change derived from the jth study for the sample size of reported animals (n_j), with k being the total number of studies.

This analysis was performed separately for the two groups without or with an MCS system.

Results

Results of Search and Included Studies

A total of 454 studies were found, and 23 trials were finally included (see Figure 1).

Animal Species

Whereas in earlier years mostly dogs were used as animal models (n = 6), nowadays pigs (n = 6) and mostly sheep (n = 11) are utilized. Average weight of the animals varied widely from 5.6 to 65 kg. In Table 2, all studies and the employed animal models are summarized.

Surgical Classification

The classification of the exclusively single one-step surgical approach was divided into two categories: first, the geometric shape of the TCPC, and second, the handling of coronary sinus blood flow.

i. The different geometric shapes of the generated TCPC structure were classified into cross-like ones (IVC and SVC were connected to the right PA, n = 5) and Y/T-shape-like ones (IVC and SVC were connected to the main PA, n = 18). The detailed results of this classification are summarized in Table 3. Additionally, surgical details such as the utilization of cardiopulmonary bypass (CPB), blood transfusions, and ventricular fibrillation are presented in Table 3. No study reported the use of cardioplegic cardiac arrest.

ii. Approaches for handling of venous coronary flow, which drains into the RA, were analyzed and classified into two groups depending on whether the main PA was

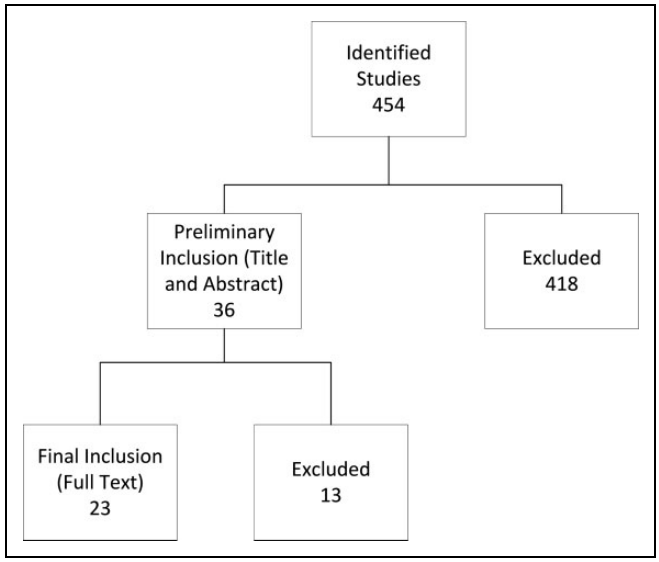

Figure 1. Inclusion process and number of reviewed manuscripts.

Table 2. Animal Species in the Included Studies With an Extracardiac TCPC.

Species	Study	Number of Animals	Weight (kg)
Canine	Kaku et al[10]	9	Range: 7.3-10.3
	Macé et al[11]	5	Mean (SD): 22.4 (1.5)
	Nawa et al[12]	5	Mean (SD): 10.6 (1.75)
	Szabo et al[13]	6	No data
	Szabo et al[14]	12	Mean (SD): 22.3 (5.2)
	Tanoue et al[15]	24	Mean (SD): 16.8 (2.7)
Ovine	Gandolfo et al[16]	6	Range: 42.0-48.0
	Koçyıldırım et al[17]	3	Mean (SD): 65.0 (4.1)
	Myers et al[18]	19	Mean (SD): 7.2 (1.1)
	Riemer et al[19]	5	Range: 42.0-48.0
	Rodefeld et al[20]	13	Mean: 56.5; range: 33.0-78.6
	Rodefeld et al[21]	13	Mean (SD): 5.6 (1.5)
	Swartz et al[22]	3	Mean (SD): 56.6 (5.7)
	Tsuda et al[23]	4	Range: 47.0-57.0
	Wang et al[24]	5	Range: 35.0-45.0
	Wang et al[25]	13	Range: 35.0-45.0
	Wang et al[26]	6	Range: 35.0-45.0
Porcine	Derk et al[27]	4	Mean:50.7; range 44.0-61.0
	Kanakis et al[28]	8	Mean (SD): 43.0 (3.8)
	Klautz et al[29]	8	Mean (SD): 28.3 (7.9)
	Macé et al[30]	8	Mean (SD): 31.4 (4.0)
	Sinha et al[31]	5	Mean: 25.0
	Wei et al[32]	5	Mean (SD): 8.8 (0.9)

Abbreviations: SD, standard deviation; TCPC, total cavopulmonary connection.

Table 3. Summary of Manuscripts With a Cross-Like and a Y/T-Like Shape of the TCPC With and Without MCS.

	Y/T-Shape/Main PA			Cross-Shape/RPA		
	Study	Surgical Details	Pump Type	Study	Surgical Details	Pump Type
Without MCS	Kanakis et al[28]			Kaku et al[10]	BT	
	Kocyildirim et al[17]			Wang et al[25]		
	Macé et al[11]	CPB, VF, BT				
	Macé et al[30]	CPB, VF, BT				
	Nawa et al[12]					
	Szabo et al[13]					
	Szabo et al[14]					
With MCS	Derk et al[27,a]		Jarvik 2000 (Jarvik Heart Inc; New York, NY, USA)	Rodefeld et al[20]	CPB, BT	Hemopump HP 24, 24F (Medtronic Inc, Minnesota)
	Gandolfo et al[16]	CPB	Jarvik child 2000	Wang et al[24,a]		Double lumen cannula (Avalon cannula [Maquet Inc, New Jersey] with CentriMag pump [Abbott, Illinois])
	Klautz et al[29]		Rollerpump (unknown)	Wang et al[26,a]		Double lumen cannula (adapted Avalon cannula with CentriMag pump)
	Myers et al[18]	BT	Paraflow (A-Med Systems West Sacramento, CA, USA)			
	Riemer et al[19,a]		HeartMate II (Abbott, Abbott Park, IL, USA)			
	Rodefeld et al[21]	BT	Paraflow			
	Sinha et al[31,a]	CPB	Rotaflow Pump (Maquet Inc, Wayne, NJ, USA)			
	Swartz et al[22]		HeartMate II			
	Tanoue et al[15]		Centrifugal pump (unknown)			
	Tsuda et al[23]		HeartMate II			
	Wei et al[32]		Impella LD (Abiomed Inc., Danvers, MA, USA)			

Abbreviations: BT, homologous blood transfusion; CPB, cardiopulmonary bypass; MCS, mechanical circulatory support; PA, pulmonary artery; RPA, right pulmonary artery; TCPC, total cavopulmonary connection; VF, ventricular fibrillation.
[a]Experiments with and without MCS.

clamped (n = 14) or not (n = 9). In case of closure of the pulmonary trunk (clamped or other modality), three different published modalities were found:

1. The left atrial appendage was anastomosed to the proximal PA. This resulted in drainage of the coronary flow ejected by the right ventricle (RV) into the left atrium against a very low pressure (n = 1).
2. The RV and/or the RA was vented to pump the coronary flow towards the left atrium, the extracardiac conduit, a blood reservoir, the jugular vein, or the SVC (n = 11).
3. An atrial septum defect (ASD) was created to guide the coronary flow from the right to the left atrium (n = 2).

Table 4 provides the detailed results of the classification into the three strategies to deal with the coronary flow.

Hemodynamic Parameters

For statistical analysis, the studies were divided into two groups: unsupported TCPC and TCPC with MCS. Studies with excessive volume loading to maintain baseline levels in hemodynamics[10–12,30] were excluded from statistical analysis.

Table 4. Classification of Studies Regarding the Coronary Flow Handling With a Closed or Open Pulmonary Artery.

Pulmonary Trunk Closed	Study	Pulmonary Trunk Left Open	Study
Vented right ventricle (n = 11)	Kaku et al[10] Kanakis et al[28] Klautz et al[29] Kocyildirım et al[17] Macé et al[11] Myers et al[18] Rodefeld et al[20] Rodefeld et al[21] Szabo et al[13] Szabo et al[14] Tanoue et al[15]	Coronary flow ejected in PA (n = 9)	Derk et al[27] Gandolfo et al[16] Riemer et al[19] Swartz et al[22] Tsuda et al[23] Wang et al[24] Wang et al[25] Wang et al[26] Wei et al[32]
ASD (n = 2)	Nawa et al[12] Sinha et al[31]		
Proximal PA anastomosed to left atrial appendage (n = 1)	Macé et al[30]		

Abbreviations: ASD, atrial septum defect; PA, pulmonary artery.

In animals with a TCPC without MCS, the CVP increased by +146% (n = 39) and the CO dropped by −42% (n = 37). Mean arterial pressure decreased by −23% (n = 37). Pulmonary arterial pressure increased by +20% (n = 44). Left atrial pressure was found to decrease by −1% (n = 34) and PVR indicated a rise of +176% (n = 34).

In animals with MCS in cavopulmonary position, the elevation of CVP was less pronounced (increase of +26%, n = 61) and the CO remained almost constant with an increase of +5% (n = 50). Left atrial pressure and PAP increased by +27% (n = 50) and +33% (n = 65), respectively, whereas MAP indicated a decrease of −15% (n = 55). Pulmonary vascular resistance did not increase as much as in the unassisted group (+48%, n = 50).

Comment

We identified 23 studies describing surgical creation of an extracardiac TCPC, all of them completed within a single surgery. Although there is a variety of successfully established acute TCPC animal models with surgical and hemodynamic results presented in the literature, none of these studies showed a successful long-term survival after establishing extracardiac TCPCs in animals with and without MCS. The longest survival was three days with MCS support from the IVC to the PA reported by Tsuda et al.[23] Nevertheless, severe complications such as pump thrombosis and sudden death were observed in this study. Graft kinking due to change of body position in the awake animal was identified to contribute to these complications. For the sake of completeness, it has to be mentioned that one abstract describing a successful long-term ovine model without MCS was recently reported with extracardiac TCPCs with a perioperative survival rate of 58%.[33]

Surgical Creation of an Extracardiac TCPC

In all the described approaches to create an extracardiac TCPC, the caval veins were connected to the pulmonary arteries and closed toward the RA to bypass the right heart. Nevertheless, the coronary venous return drains into the RA. There are several surgical options for handling of the coronary flow.

With the pulmonary trunk left open (n = 9), the coronary venous return is ejected by the RV toward the PA. No substantial hemodynamic effect such as additional pulsatility is expected due to the small contribution of the coronary blood flow compared to the total volume flow through the lungs.[16]

If a closure of the pulmonary trunk prevents the RV to eject blood toward the pulmonary circulation, a further intervention is necessary to ensure drainage of the venous coronary flow. The most common and simple approach is the placement of a vent into the RA/RV (n = 11) to pump the coronary blood flow to the right heart bypass or to any other blood vessel. Another solution is the surgical creation of an ASD (n = 2), where the use of CPB seems necessary. A third approach is anastomosing the proximal PA to the appendage of the left atrium,[30] which is time-consuming and technically demanding.

Selection of the proper animal model may play an important role for a complete Fontan circulation since e.g. in pigs and in sheep, the left vena azygos drains directly into the coronary sinus.[34,35] None of the studies mentioned a ligation of the left vena azygos; however, it remains open to which extent this fact compromises the hemodynamic condition or the measurement of important cardiovascular parameters such as the CO or coronary venous flow.

In this study, we found that the connection of the caval veins to the main PA (Y/T shape) is the most common approach (n = 18), followed by the connection to the right PA (cross-like shape; n = 5). Creating a bidirectional cavopulmonary anastomosis (=Glenn anastomosis) in sheep is surgically more challenging than connecting the SVC to the pulmonary trunk as the

distance to the right PA is much longer compared to humans. All artificial connections for the creation of the TCPC add additional hydraulic resistance and impair venous return: In general, the longer, the thinner, and/or the more curved the connections, the higher the resistance. Consequently, realistic shapes and geometries of these connections are required to achieve hydraulic TCPC properties that make results applicable and comparable to human TCPC conditions.

The surgical procedure to create a TCPC in animal models needs to be selected based on the purpose of the experiment. Whereas most cardiovascular research mainly requires realistic hemodynamics, in animal models focusing on MCS, a realistic TCPC geometry might be mandatory, especially if devices are designed for the geometry of the cavopulmonary junction.[24,26,36]

Hemodynamic Observations

In all studies with nonassisted univentricular physiologies, an expected immediate drop in CO and an increase in CVP at the transition of the biventricular to the univentricular circulation were evident. The major limitation seems to be a significant, intraoperative increase of PVR. The effects of the elevated PVR are decreased venous return, insufficient filling of the systemic ventricle, low CO, and high CVP.

Theoretically, two approaches are intuitive to resolve the limiting hemodynamic effects of the elevated PVR: either the CVP needs to be increased or the PVR decreased. In earlier years, a "corset" was described to prevent fluid from accumulating in the splanchnic space by mechanic compression,[10] thereby increasing the CVP. Another possibility to increase the CVP is the additional application of homologous blood or other colloids[10–12,30] to add volume, while keeping the colloid osmotic pressure in a physiologic range and preventing potential edema formation.

Lowering PVR can be achieved by pharmacological interventions with, for example, nitric oxide (NO), sildenafil, and/or prostaglandins. None of these substances for treatment of high PVR was investigated in the analyzed studies.

There are several potential causes for the (initial) increase of PVR: Well-known contributors to an elevated PVR are the use of CPB, response to anesthesia, surgical trauma, and mechanical ventilation.[16] Further, the decrease in CO in the univentricular condition may result in a hypoperfusion of the pulmonary capillary vasculature[28] and consequently derecruitment of pulmonary capillaries. The adaptation of PVR by recruitment of pulmonary capillaries could also explain the fact that in the MCS group (with a normalized CO) PVR only increased by +48% versus +176% in the unsupported group. In one study with cavopulmonary support using a Jarvik 2000 Child Pump, the PVR did not increase at all.[16]

Mechanical Circulatory Support Considerations

A wide range of MCS systems was used to investigate the effects of MCS in the univentricular circulation: roller, axial, and radial pumps were employed. In all but one study, an MCS device was placed in cavopulmonary position. Only Sinha et al[31] assisted the circulation by pumping blood from the common atrium to the ascending aorta.

None of the MCS systems was specifically designed for the challenges of the Fontan circulation. Implantation seems challenging and only possible with additional conduits, which are prone to kinking.[23] Besides thromboembolic events,[23] collapse of the caval veins was among the complications reported.[19,37] It is worth noting that Gandolfo et al showed that an adaptation of the hydraulic characteristics of the implanted pump to the low pressure conditions in the cavopulmonary circulation reduced the risk of venous collapse.[16]

With MCS it was possible to restore CO, however, at the expense of an increased LAP. This may be explained by a deteriorating cardiac function due to the invasive surgery and/or the different loading of the RV in the univentricular state, which can lead to a septum shift and thus to an impairment of the ventricular function.

All these challenges underline the need for novel assist devices that are perfectly tailored to cavopulmonary support. Probably such devices have to be physiologically controlled to adapt the output to the need of the patient with the aim to prevent excessive overpumping with potential collapse of vasculature as well as pulmonary edema or undersupply of the cardiovascular system.[37]

Future Perspectives

The results of this review show that it remains questionable whether a standardized chronic univentricular animal model can be established within a single surgical procedure. Similar to the stepwise procedure in humans, a gradual adaptation of the cardiovascular system to the altered hemodynamic condition may be an option for an animal model. Different attempts to establish parts of the Fontan circulation using a transcatheter approach alone[38,39] or in a combined surgical preconditioning and completing interventional approach[40-48] have been reported during the last two decades. Such a procedure would reduce the risk of reoperation (especially bleeding and injuries to lungs and heart) and a second CPB run could be avoided, which is certainly beneficial for cardiac function. If such an attempt is taken in animals, it is important to consider the different anatomical prerequisites in comparison to the human anatomy,[49] such as the different anatomical relation of the SVC to the right PA, the angulation of the axis IVC-RA-SVC, as well as the pulmonary venous drainage in the space in-between the SVC and right PA in sheep and calves.[49] Still, it has been shown that interventional creation of a superior cavopulmonary connection with the usage of long covered stents,[39] intervascular connections as the interventional Potts shunt,[50] or interventional completion of Fontan are possible in animals and also in humans.[40,42-48,51]

The different anatomical features in animals and the nowadays limited availability of endovascular catheter materials make the creation of a solely interventional superior

cavopulmonary connection difficult. Most likely, such a procedure will result in a connection between the SVC and the right lower lobe PA, directing most of the blood flow to the right lower lobe. The question whether such an approach is sufficient for a chronic (hemi-) Fontan animal model remains open to debate.

In view of cardiac catheter materials/implants, inspiration comes from gastrointestinal interventions. "Spool-shaped" or "trumped-shaped" covered stents, as well as long self-expandable covered stents or endoprosthesis seem to provide new technical options in the creation of a transcatheter superior cavopulmonary connection and subsequently also the TCPC in the near future.[52] Transcatheter interventional creation of an ASD to handle coronary sinus blood flow seems an important and relatively easily feasible addition to the procedure, being less invasive compared to surgical ASD creation. In a next step, the authors plan to prove the concept to establish a Fontan circulation using a hybrid approach to realize a chronic animal model with an extracardiac TCPC.

Conclusion

Despite presence of a large variety of surgical procedures to create an extracardiac TCPC in animals in the literature, establishing a univentricular circulation in one single step remains challenging. Acute TCPC animal models were successfully established with and without MCS reflecting the most important hemodynamic features of a Fontan circulation; however, no chronic animal model was identified in this review. This calls for novel approaches to complete a Fontan circulation in animals. Approaches facilitating a stepwise adaptation of the cardiovascular system to the altered hemodynamic condition may be a promising alternative. A combined preconditioning surgical and transcatheter procedure to create a chronic Fontan animal model may have the potential to overcome the limitations of a solely surgical TCPC completion in one step.

Authors' Note

Marcus Granegger and Anna Valencia contributed equally to the manuscript.

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